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REVIEW

CANCER INNOVATION

Advances and prospects of drug clinical research in colorectal cancer in 2022

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Abstract

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death worldwide. Clinical research results have provided more treatment opportunities for CRC patients, showing that an optimal combination of existing drugs and new drugs is needed to mitigate the burden of this disease. In this review, we have summarized recent advances in drug clinical research for CRC in 2022, including chemotherapy, targeted therapy, and immunotherapy, to find opportunities for substantial improvements in drug discovery and clinical development methods.

KEYWORDS

colorectal cancer, chemotherapy, targeted therapy, immunotherapy

1 | INTRODUCTION

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths globally and accounts for 10% of cancer incidences worldwide [1, 2]. Its prevalence is increasing around the globe. In China, the incidence and mortality of CRC were ranked second and fourth, respectively [3]. The development of fluorouracil in 1962 marked a new epoch in antitumor drug treatment for CRC. Moreover, molecularly targeted therapy and immunotherapy have also offered new therapeutic strategies for patients in recent years. Statistically, more than 900 clinical research projects in CRC are currently underway worldwide, involving chemotherapy, targeted therapy, immunotherapy, and other means. This article

Abbreviations: AACR, American Association For Cancer Research; AEs, adverse events; ASCO, American Society of Clinical Oncology; CRC, colorectal cancer; CRCLMs, colorectal cancer liver metastases; CSCO, Chinese Society of Clinical Oncology; DCR, disease control rate; dMMR, mismatch repair deficiency; DOR, duration of response; DpR, depth of response; EMA, The European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, The US Food and Drug Administration; HRQoL, health-related quality of life; ICIs, immune checkpoint inhibitors; ITT, intention-to-treat; mDDC, median duration of disease control; MSI-H, high microsatellite instability; MSS, microsatellite stable; NCCN, National Comprehensive Cancer Network; NED, no evidence of disease; ORR, objective remission rate; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; PFS2, time from randomization to second progression or death; RR, response rates; TKI, tyrosine kinase inhibitor.

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aims to review the clinical research on the treatment of CRC in 2022 (Table 1).

2 | CHEMOTHERAPY FOR CRC

Research progress in chemotherapy for CRC was slower compared with targeted therapy and immunotherapy. However, emerging clinical research data have been reported on conversion therapy, maintenance therapy, and sequential treatment, which provides clinicians with new therapeutic evidence for CRC.

2.1 | Conversion systemic chemotherapy for CRC

Only 10%–20% of patients with colorectal cancer liver metastases (CRCLMs) can undergo radical resection at diagnosis [21]. Conversion therapy can convert 10%–30% of patients with initially unresectable lesions to surgical resection with effective systemic therapy, and the 5-year overall survival (OS) rate can be increased to more than 55% [22]. Therefore, this therapy has become a research focus; it can improve the long-term prognosis of metastatic colorectal cancer (mCRC) patients by increasing the radical resection rate of CRCLMs.

There is consensus on the efficacy of the combination of chemotherapy with targeted therapy. The BECOME study [23] is the first clinical study to confirm that chemotherapy plus bevacizumab increased the radical resection rate of liver metastases and markedly increased OS and progression-free survival (PFS) in CRCLM patients with the RAS mutant. However, CRC patients with the BRAF V600E mutation have a poor prognosis, with a median OS (mOS) of only 20 months [24]. In contrast to triple-agent chemotherapy, the FOCULM study [25] found that the combination of cetuximab with mFOLFOXIRI significantly increased the rate of no evidence of disease and the objective response rate (ORR) in patients with unresectable CRCLMs. This study provided a new treatment strategy for CRC patients with unresectable liver metastases and wild-type RAS/BRAF, which filled the blank.

According to the TRIPLETE study [4] published by the American Society of Clinical Oncology (ASCO) in 2022, the use of the combination of panitumumab and three drugs yielded ORR and R0 resection rates comparable with those of the combination of panitumumab and double-agent chemotherapy. However, for patients with high tumor burden, poor prognosis, poor translational outcome, and requiring translational therapy immediately, the combination of anti-EGFR antibodies and triple-agent chemotherapy may be the best choice.

The CAIRO5 study [5], a multicenter, randomized, phase III trial presented at ESMO in 2022, enrolled patients with CRCLMs and carried out genetic testing to identify RAS and BRAF mutational status. This clinical study primarily presented the results of patients with left-sided and wild-type RAS/BRAFV600E tumors who were randomized to be treated with chemotherapy plus either bevacizumab (arm A) or panitumumab (arm B), with a median follow-up of 44 months. Between arm A and arm B, no significant differences were found in the median progression-free survival (mPFS) (10.6 m vs. 10.3 m, $p = 0.44$) and the R0/1 ablation rate (58% vs. 56%, $p = 0.79$), but there were differences in ORR (52% vs. 76%, $p < 0.01$), median depth of response (33% vs. 49%, $p < 0.01$), and grade ≥3 toxicity (52% vs. 69%, $p = 0.01$). In general, for unresectable CRCLMs patients with wild-type RAS/BRAF-V600E, there was no difference in mPFS on treatment with bevacizumab or panitumumab in combination with FOLFOX/FOLFIRI as the first-line therapy, and panitumumab combination therapy did not lead to improvements in the local treatment rates of CRCLMs patients, which induced a higher incidence of adverse events (AEs).

2.2 | Maintenance chemotherapy for CRC

Patients who benefit from first-line standard chemotherapy or combination targeted therapy have three treatment options: continuous therapy, maintenance therapy, and intermittent therapy [26]. The aim of maintenance is to prolong both the remission duration and the OS, and patients can stop high-intensity first-line treatment and convert to using low-intensity, low-toxicity agents for ongoing treatment when the disease is stable [26]. This is the most effective strategy among the three treatment options for extending PFS, reducing adverse effects, and delaying the time to recurrence.

The OPTIMOX-1 study [27] found that maintenance therapy was as effective as continuous therapy, but it had fewer adverse effects. The OPTIMOX-2 study [28] found that maintenance therapy was significantly more effective than intermittent therapy, with no difference in toxicity or quality of life. A series of large phase III randomized-controlled studies have demonstrated the feasibility and safety of maintenance therapy (capecitabine alone or in combination with bevacizumab), all of which provided high-level evidence for maintenance therapy.

TABLE 1 2022 overview of clinical trials in colorectal cancer.

Clinical study	Phase	Patients	Treatment	ORR (%)	mPFS (months)	mOS (months)
TRIPLETE [4]	III	RAS and BRAF wt mCRC	mFOLFOX6 + PANI vs. mFOLFOXIRI + PANI		12.7 vs. 12.3	
CAIRO5 [5]	III	RAS/BRAFV600E wt mCRC	FOLFOX/FOLFIRI + Bev vs. FOLFOX/FOLFIRI + PANI		10.6 vs. 10.3	
ERMES [6]	III	RAS and BRAF wt mCRC	FOLFIRI + Cet until PD/toxicity vs. FOLFIRI + Cet for eight cycles, followed by Cet alone		mPP: 12.2 vs. 10; ITT: 10.7 vs. 9	mPP: 30.7 vs. 36.6; ITT: 25.3 vs. 31
IMPROVE [7]	II	RAS/BRAF wt mCRC	Continuous FOLFIRI + PANI vs. intermittent FOLFIRI + PANI	64 vs. 56	12.6 vs. 17.6	
STRATEGIC-1 [8]	III	RAS/BRAF wt mCRC	Line1: FOLFIRI-Cet + Line2: mFOLFOX6-Bev vs. Line1: FOLFOX-Bev + Line2: FFOLFIRI-Bev	Line1: 82.5 vs. 65.9 Line2: 21.2 vs. 17.2		
BREAKWATER [9]	III	BRAF V600E-mut mCRC	Encorafenib + Cet + chemotherapy	19.50	4.3	
NCT04017650 [10]	I/II	BRAF V600E-mut and MSS	Encorafenib + Cet + NIVO		7.3	11.4
SEAMARK [11]	II	BRAF V600E-mut and MSI-H/dMMR CRC	Pembrolizumab + encorafenib + Cet vs. pembrolizumab			
NCT04449874 [12]	IA	KRAS G12C-mut CRC	Sotorasib + PANI	30		
KRYSTAL-1 [13]	I/II	KRAS G12C-mut CRC	MRTX849 + Cet vs. MRTX849	19 vs. 46	5.6 vs. 6.9	
HERACLES-A [14]	II	HER2 + mCRC	Tucatinib + trastuzumab	38.1	8.2	24.1
MOUNTAINEER [15]	II	HER2 + mCRC	Tucatinib + trastuzumab	52.20	8.1	18.7
NICHE 2 [16]	III	dMMR				
KEYNOTE-177 [17]	III	dMMR/MSI	Pembrolizumab vs. mFOLFOX6/FOLFIRI ± Bev/Cet		16.5 vs. 8.2	36.7 vs. 27.3
SAMCO-PRODIGE 54 [18]	II	dMMR/MSI	Chemotherapy ± targeted vs. ave	28 vs. 30		
CheckMate142 [19]	II	dMMR/MSI	NIVO vs. NIVO + IPI Q3W followed by NIVO Q2W vs. NIVO Q2W + IPI Q6W	39 vs. 65 vs. 71	13.8 vs. NR vs. NR	44.2 vs. NR vs. NR
COMMIT [20]	III	dMMR/MSI	Atezo vs. mFOLFOX6/Bev + Atezo			

Abbreviations: Bev, bevacizumab; Cet, cetuximab; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; ITT, intention-to-treat; mCRC, metastatic colorectal cancer; mOS, median overall survival; mPFS, median progression-free survival; mPP, modified per-protocol; MSS, microsatellite stable; Mut, mutant; NR, not reached; ORR, objective remission rate; PANI, panitumumab; PD, progressive disease; Wt, wide-type.

The fluorouracil ± bevacizumab protocol is the standard maintenance treatment regimen for mCRC [29, 30]. However, for mCRC patients with wild-type RAS/BRAF who have achieved disease control after first-line induction therapy with FOLFIRI combined with anti-EGFR antibodies, how to choose the best maintenance therapy is still inconclusive [31].

The ERMES study [6] is a multicenter, noninferiority, randomized, phase III trial that aimed to explore the noninferiority and safety of maintenance therapy for anti-EGFR monotherapy combined with chemotherapy versus continuous therapy with FOLFIRI plus cetuximab for patients with unresectable wild-type RAS and BRAF mCRC. Unfortunately, in the intention-to-treat (ITT) population, the mPFS was 9 months in the monotherapy group versus 10.7 months in the continuous combination therapy group (HR = 1.1, 95% confidence interval [CI]: 0.92–1.31, $p = 0.39$), failing to confirm the noninferiority of these two groups for PFS. According to safety assessments, the cetuximab monotherapy maintenance therapy group had a decreased incidence of grade 3 AEs. Furthermore, survival analysis suggested that cetuximab monotherapy may have better efficacy in specific patient groups, and biomolecular marker analyses are underway to determine the optimal patient population that can benefit from this strategy. It is worth noting that the ERMES study did not include a group treated with single-agent fluorouracil combined with cetuximab, and comparative efficacy results with the single-agent cetuximab treatment arm are also of interest.

2.3 | Sequential treatment for CRC

The treatment of mCRC involves a multifaceted approach that includes chemotherapy, antiangiogenic therapy, and anti-EGFR antibodies. However, the emergence of drug resistance and treatment-related toxicity limits the lasting effectiveness, and sequential strategies can reduce toxicity and chemoresistance. 2022 ASCO yields exciting clinical findings that may aid clinicians in their treatment modalities for mCRC research.

IMPROVE [7], a randomized, open-label, multicenter phase II study, enrolled unresectable, previously untreated wild-type RAS/BRAF mCRC patients. The continuous treatment group received FOLFIRI/panitumumab until the disease progressed. The intermittent treatment group received eight cycles of the same regimen, followed by a treatment-free interval, which lasted until progressive disease when another treatment period of up to eight cycles was restarted. The intermittent treatment group demonstrated a trend toward a more pronounced survival benefit, with a high mPFS of 17.6 months and a 1-year PFS rate of 61.3%, compared with 12.3 months and 51.7%, respectively, in the continuous treatment group. In terms of safety, the intermittent strategy led to a lower rate of severe skin toxicity and fewer treatment discontinuations due to AEs. In addition to ensure the life quality of patients and improve efficacy, intermittent treatment also cuts the cost of care. Although the study results are encouraging, evidence from additional phase III studies with larger samples is needed for the clinical application of the intermittent treatment.

The STRATEGIC-1 study [8] was the first to evaluate the optimal strategy for multiple lines of standard therapy in mCRC patients with wild-type KRAS/NRAS/BRAF. The study included 263 patients in total, who were randomly divided into two groups. Group A received FOLFIRI + cetuximab in the first line and mFOLFOX6 + bevacizumab in the second line, while group B received FOLFOX + bevacizumab in the first line, FOLFIRI + bevacizumab in the second line, and anti-EGFR antibody ± irinotecan treatment. The findings suggested that FOLFIRI + cetuximab used in the first line and mFOLFOX6 + bevacizumab used in the second line yielded higher ORR (21.2 m vs. 17.2 m, $p = 0.541$) in mCRC patients with wild-type RAS/BRAF and an mOS breakthrough of 3 years (37.8 m vs. 34.4 m, $p = 0.121$), but the median duration of disease control performance was similar in both groups (22.5 m vs. 23.5 m, $p = 0.805$).

3 | TARGETED THERAPY FOR CRC

With advancements in molecular targeted therapy-related studies, biomarker-based targeted therapy has provided more options and longer benefits to patients with mCRC. Gene mutations or molecular features have received increasing attention, and several therapeutic targets besides previously known RAS and BRAF provide novel strategies for the treatment of CRC, such as the KRAS G12C mutation, HER2 amplification, and RAS/MAPK pathway activation. The results of some new clinical studies focusing on the above targets have been reported this year. The following will describe the clinical research progress of targeted therapy for CRC.

3.1 | BRAF V600E-mutated CRC

BRAF mutations are present in approximately 10%–15% of patients with mCRC, and the V600E mutation is the most common mutation type [32]. Due to lower response rates to traditional chemotherapy and a worse prognosis,

the treatment development for patients with the BRAF V600E mutation has received considerable attention. Current inhibitors targeting BRAF include encorafenib, vemurafenib, dabrafenib, and so on.

The updated analysis of the BEACON study [33] confirmed the significant value of the anti-EGFR antibody plus the BRAF inhibitor. As a randomized, phase III trial, the aim of the study was to evaluate the efficacy and safety of encorafenib, binimetinib plus cetuximab (triplet) versus encorafenib plus cetuximab (doublet) versus irinotecan plus cetuximab or FOLFIRI plus cetuximab (control) in patients with BRAF V600E mutant mCRC. The primary endpoints were OS and independently reviewed ORR. Both the triplet and doublet groups showed improved OS compared with the control group. The mOS was 9.3 months for the triplet group ($n = 224$) and 5.9 months for the control group ($n = 221$), with a 40% reduction in the risk of death. The mOS for the doublet group ($n = 220$) was 9.3 months, with a 39% reduction in the risk of death compared with the control group. The ORR was 26.8% for triplet group, 19.5% for doublet group, and 1.8% for the control group. AEs were consistent with previous analyses. The incidence of grade 3 AEs was 65.8%, 57.4%, and 64.2% for the triplet group, the doublet group, and the control group, respectively. Although both triple therapy and dual therapy improve OS, dual therapy has a superior safety profile, which has allowed the regimen to be approved by the US Food and Drug Administration and the European Medicines Agency. The dual therapy had a superior safety profile and changed guidelines and clinical practice for mCRC patients with the BRAF V600E mutation, making anti-BRAF + anti-EGFR therapy the standard second-line treatment, even though the improvement in OS was outstanding for both triple and dual targeted combinations. For patients with BRAF V600E-mutated mCRC, the BEACON trial pioneered second-line chemotherapy-free targeted therapy. Nonetheless, the ideal first-line treatment regimen is still uncertain. BREAKWATER [9] is an ongoing phase III trial designed to evaluate the curative effect of cetuximab plus encorafenib with/without chemotherapy versus standard first-line chemotherapy for patients with BRAF V600E-mutated mCRC. With the planned enrollment of 290 patients in each group, the primary study endpoint was PFS comparing cetuximab plus encorafenib with/without chemotherapy versus chemotherapy with/without bevacizumab. The European Society for Medical Oncology (ESMO) released the safety import data of the study this year, and the preliminary ORR of cetuximab plus encorafenib combined with FOLFOX6 or FOLFIRI was satisfactory, approaching 70%. This treatment regimen's duration of response (DOR) was very impressive. Further follow-up of PFS and OS data is needed.

We look forward to further exploring the effect of precision-directed combination therapy with the results of breakthroughs in posterior line treatment, providing more possibilities for first-line treatment and benefiting patients with the BRAF V600E mutation.

In addition, another population that requires attention for their favorable clinical response with immunotherapy is patients with the BRAF V600E-mutated and mismatch repair deficient (dMMR)/microsatellite instability high (MSI-H) tumors, as was seen in the existing KEYNOTE and CheckMate series clinical studies. Immunotherapy, therefore, is recommended as the preferred treatment for such patients. ASCO published a phase I/II trial of cetuximab plus encorafenib combined with nivolumab in postline patients with the BRAF V600E mutant and microsatellite stable (MSS). The results showed that the ORR was 50%, the disease control rate (DCR) was 96%, mPFS was 7.4 months, and mOS was 15.1 months, with the value of further exploration [10]. Another ongoing phase II trial, SEAMARK [11], aims to compare the efficacy of first-line cetuximab plus encorafenib combined with pembrolizumab versus pembrolizumab monotherapy for patients with the BRAF V600E mutation and dMMR/MSI-H mCRC. The study is still in the enrollment phase, and the results are worth expecting.

Barras et al. [34] confirmed the heterogeneity in colorectum tumors with the BRAF V600E mutation by analyzing gene expression data of two tumor subtypes with different molecular patterns, therapeutic targets, and prognoses from CRCLMs patients with the BRAF V600E mutation. Patients with BRAF V600E mutations may have more treatment options based on precision-combination therapies.

3.2 | KRAS mutations CRC

Activating KRAS mutations are the first predictive negative biomarker for response to anti-EGFR therapies in mCRC, with mutations in approximately 40% of all mCRC cases [35]. KRAS was historically considered an undruggable target for a long time, but the emergence of inhibitors targeting the KRAS G12C mutation has changed this situation, bringing evangel to patients with the KRAS mutation. The prevalence of the KRAS G12C mutation is approximately 2%–3% in Chinese CRC patients [36]. In recent years, several small-molecule targeted agents targeting KRAS G12C and G12D

mutations have been under preclinical development and/or clinical evaluation.

The 2022 ESMO reported a clinical study (NCT04449874) [37] that aims to evaluate the safety, antitumor activity, and pharmacokinetics of GDC-6036 monotherapy or combination therapy in KRAS G12C-mutation solid tumors. The ORR of monotherapy in KRAS G12C-mutated mCRC was 24%, with satisfactory safety. The CodeBreaK100 multicohort study [12] was a phase I/II trial of KRAS G12C inhibitor sotorasib (AMG 510) in advanced CRC, with an ORR of 9.7% and a DCR of 82.3%, mPFS of 4.0 months, and mOS of 10.6 months. Furthermore, 2022 ESMO also reported the phase Ib expansion cohort data of sotorasib combined with panitumumab in the treatment of refractory KRAS G12C-mutant mCRC. The results showed that the ORR was 30% without regard to tumor site, DCR was 93%, mPFS was 5.7 months, and mOS had not been reached after nearly 9 months of follow-up [37]. According to the currently published survival curves, the efficacy could be better than the current third-line standard treatment. Therefore, multitarget combination therapy would be a more effective strategy for patients with KRAS G12C-mutant mCRC. Additionally, the CodeBreaK300 phase III study [38] comparing sotorasib combined with panitumumab versus chemotherapy and the CodeBreaK101 study [31] investigating the efficacy of sotorasib plus panitumumab and the FOLFIRI regimen for first-line treatment is currently in progress and the results are eagerly awaited.

The updated results about another KRAS G12C inhibitor adagrasib (MRTX849) were also released in 2022 ESMO, demonstrating that the ORR was 19% and the DCR was 86%, mPFS was 5.6 months, and mOS was 19.8 months in the postline monotherapy patients with KRAS G12C-mutant mCRC, while in patients treated with cetuximab plus adagrasib, the ORR, DCR, mPFS, and mOS were 46%, 100%, 6.9 months, and 13.4 months, respectively [13], which indicated promising clinical efficacy.

The prevalence of the KRAS G12D mutation is approximately 50% in patients with CRC, but there have never been any effective drugs for this target. A novel, selective, noncovalent, high-affinity KRAS G12D inhibitor, MRTX1133, can bind to both inactivated and activated KRAS G12D mutants and selectively inhibit KRAS-dependent signaling pathways to achieve antitumor effects. HRS-4642 with the same target has also been explored for treating patients with advanced solid tumors harboring the KRAS G12D mutation. Whether it can be promoted to clinical practice is worth looking forward to.

3.3 | HER2-amplified CRC

HER2 is another target that needs to be considered in the CRC. The prevalence of HER2 amplification and the HER2 mutation in CRC patients is about 5%, which may predict poor response to the anti-EGFR monoclonal antibody. Currently, HER2-targeting agents mainly include small molecules, monoclonal antibodies, bispecific antibodies, and ADC drugs.

In the MyPathway basket study [39], the ORR and DCR of trastuzumab combined with pertuzumab reached 32% and 44%, and the mPFS was only 2.9 months, but the mOS was 11.5 months in the postline treatment of mCRC. The results highlighted that the dual HER2-targeting agents could be a viable option for patients with HER2-positive mCRC. Patients with wild-type RAS/BRAF and HER2-amplified advanced CRC, who cannot be treated with standard treatment, were enrolled and treated with trastuzumab plus pertuzumab in the TRIUMPH study [40]. Among the enrolled patients, 80% had received ≥3 lines of treatment before. The ORR of this regimen in the study was about 30% and the mPFS was about 4 months. In the HERACLES-A study [14], the ORR and PFS of trastuzumab combined with lapatinib in the same patient population were also consistent with the previous studies.

The MOUNTAINEER study of trastuzumab plus tucatinib provides the best data, with an mPFS of 8.2 months and an mOS of 24.1 months [15]. Therefore, multidrug combination therapy strategies should also be considered for HER2-targeting agents. Additional analysis from the MOUNTAINEER study reported in 2022 ESMO demonstrated that sustainable benefits and good tolerance were observed in most patients treated with tucatinib monotherapy. While tucatinib plus trastuzumab could be more effective, in the 84 patients treated with combination therapy, the ORR was 38.1% (95% CI: 27.7%–49.3%), and DOR was 12.4 months (95% CI: 8.5–20.5), without triggering an increase in adverse reactions [41]. However, other combinations, such as pertuzumab plus T-DM1, have shown limited efficacy.

DS-8201, as a star HER2-targeting agent, is still receiving particular attention. The DESTINY-CRC01 study [42] reported that the ORR of patients with HER-2 IHC 3+ or IHC2+/ISH+ and treated with DS-8201 was 45.3%, while the ORR of patients with HER-2 low expression was 0. The mPFS of IHC 3+ patients was 6.9 months and the mOS was 15.5 months. Therefore, DS-8201 treatment for HER2-positive mCRC patients deserves expecting. In addition, in a retrospective study, pyrotinib has also been explored in CRC, and the ORR of patients treated with pyrotinib monotherapy was 33% [43]. In the HER2-FUSCC-G study [44], in HER2-positive

mCRC patients treated with pyrotinib plus trastuzumab, the ORR was 57.1% in RAS wild-type patients. However, the overall ORR of pyrotinib plus trastuzumab was 50%, and the efficacy needs to be further improved.

Zanidatamab (ZW25) is a bispecific antibody targeting HER2, which could bind to two different sites of the HER2 target simultaneously and has shown durable antitumor activity in a variety of HER2-overexpressing tumors. The results of a phase I study (NCT02892123) were announced at ASCO-GI in 2021. The study enrolled 63 patients with HER2-positive gastroesophageal adenocarcinoma that progressed on standard therapy; 35 patients received zanidatamab alone and 28 patients received zanidatamab plus chemotherapy. Zanidatamab had a single-agent ORR of 33%, DCR of 61%, and a median DOR (mDOR) of 6.0 months, while an ORR of 54%, DCR of 79%, and mDOR of 8.9 months were found in the combination therapy group, with most AEs being grade 1/2. At the 2022 ASCO meeting, the Zymeworks company released the detailed data of the HERIZON-GEA-01 study [45]; dual HER2-targeted antibody ZW25 plus tilelizumab combined with chemotherapy yielded an ORR of 75.8% and a DCR of 100% in patients with gastric/gastroesophageal junction adenocarcinoma treated in the first line. Studies on HER2-positive mCRC are mainly focused on exploring dual HER2-targeted therapy and ADCs, and a variety of HER2-targeted inhibitors are under development with excellent potential.

3.4 | Emerging drug targets for CRC

At the 2022 American Association For Cancer Research annual meeting, the most noteworthy new drugs in the field of CRC were the ERK1/2 inhibitor ERAS-007 and the SHP2 inhibitor ERAS-601 from ERASCA company [46]. When combined with encorafenib plus cetuximab, ERAS-007 showed superior antitumor activity in patients with BRAF V600E mutations compared with dual-target regimens. Similarly, promising therapeutic activity was observed when ERAS-007 was combined with palbociclib in patients with KRAS G13D and G12V mutant subtypes of CRC. ERAS-007 has shown promising clinical activity as monotherapy and combination therapy in a wide range of RAS/MAPK pathline-driven CRC models, supporting further exploration in the clinic. The preliminary results from the ongoing phase Ib/II study, HERKULES 3 (NCT05039177), evaluating the efficacy and safety of ERAS-007 in combination with encorafenib plus cetuximab or palbociclib in patients with BRAF V600E or RAS mutant CRC, are expected to be available in 2024, which is eagerly anticipated.

At the same time, ERAS-601, the SHP2 inhibitor developed by ERASCA company, has also attracted attention. ERAS-601 in combination with sotorasib or adagrasib showed promising therapeutic activity in KRAS G12C-mutant subtypes in both colorectal and lung cancer models. Besides, in "triple wild-type" (KRAS/NRAS/RAF) CRC models, ERAS-601 plus cetuximab also showed promising therapeutic activity. We optimistically anticipate the ongoing FLAGSHP-1 (NCT04670679) phase I/Ib study to evaluate the efficacy and safety of ERAS-601 alone or in combination with cetuximab in the treatment of solid tumors.

4 | IMMUNE CHECKPOINT INHIBITORS (ICIs) FOR CRC

Immunotherapy has made rapid progress in CRC, especially in MSI-H/dMMR CRC, which can benefit significantly from ICIs, and the long-term efficacy of immunotherapy has been confirmed. Current clinical research on immunotherapy for CRC includes postline, second-line, first-line, and even neoadjuvant therapy or postoperative adjuvant therapy. Some results of these clinical research have led to changes in clinical practice and have been recommended as the standard treatment for dMMR/MSI-H mCRC. However, immunomonotherapy is basically ineffective in most patients with MSS CRC. How to break through the bottleneck of MSS CRC treatment and turn the "cold tumor" of MSS into a "hot tumor" similar to MSI-H is a hot topic of exploration. By now, combined therapy is still the main direction [47].

4.1 | Systemic therapy for MSI-H CRC

4.1.1 | Neoadjuvant therapy for CRC

In the NICHE 2 study [16] of dual-ICI therapy (anti-PD-1 plus anti-CTLA-4) in patients with dMMR locally advanced CRC who received neoadjuvant therapy, patients received two doses of nivolumab and one dose of ipilimumab before surgery. The results indicated that 107/107 (100%) of patients received surgery and achieved R0 resection, and 72/107 patients (67%) achieved a pathological complete response (pCR). Whether the benefits of time-prolonged neoadjuvant immunotherapy can further improve the pCR rate remains uncertain but merits further investigation. A trend of excluding chemotherapy in treatment has been observed among these patients. Therefore, there is an urgent need to evaluate the efficacy posttreatment. Immunotherapy will

become the standard neoadjuvant therapy for patients with dMMR CRC.

4.1.2 | First-line therapy for CRC

In the first published PFS analysis of the KEYNOTE-177 study [17] of patients with advanced dMMR/MSI-H CRC, the mPFS was almost doubled in the pembrolizumab monotherapy as first-line therapy group compared with the chemotherapy with/without targeted drug group (16.5 months vs. 8.2 months). The subsequent results indicated that patients in the pembrolizumab monotherapy group presented better survival time from randomization to second progression or death, 3-year OS rates, and health-related quality of life compared with those in the chemotherapy group [48, 49], changing the treatment status of advanced CRC and being recommended as the standard treatment by the National Comprehensive Cancer Network and the Chinese Society of Clinical Oncology.

4.1.3 | Second- and postline therapy for CRC

In the SAMCO-PRODIGE 54 randomized phase II study [18] reported at 2022 ESMO, patients were randomly assigned (1:1) to receive standard second-line therapy (chemotherapy with/without targeted agents, group A) or avelumab monotherapy (group B). At a median follow-up of 33.3 months (28.3–34.8 months), the PFS of group B was superior to that of group A ($p = 0.025$), with 12-month PFS rates of 31% versus 19%, 18-month PFS rates of 27% versus 9%, and similar ORRs of 28% versus 30% ($p = 0.45$). Among patients with controlled disease, 75% of patients in group B achieved sustained disease control at 18 months, compared with 20% in group A, and the rate of treatment-related grade ≥3 AEs was 31.7% in group B versus 53.1% in group A. The SAMCO-PRODIGE 54 study confirmed that patients with dMMR/MSI-H mCRC could benefit more from second-line immunotherapy with the PD-L1 inhibitor avelumab than standard therapy. Second-line treatment with avelumab can lead to better PFS benefits in dMMR/MSI-H mCRC patients.

The KEYNOTE-164 study [50] enrolled patients with advanced MSI-H CRC who were treated with ≥2 prior lines of standard therapy (cohort A) and ≥1 prior line of standard therapy (cohort B), and these patients received pembrolizumab for up to 2 years until progression. The result suggested that after a median follow-up of 5 years, the ORRs of cohort A and cohort B were 32.8% and 34.9%, and the mOS rates were 31.4 and 47 months, respectively. The mDOR was not reached in cohort A and cohort B, and the 3-year sustained response rate was 93%. In addition, the KEYNOTE-164 study allowed 17 cycles of the anti-PD-1 antibody to be restarted after progression, which resulted in two of nine patients achieving partial remission again, six patients having stable disease, and an effective duration of more than 12 months. The KEYNOTE-164 study indicated the durable antitumor activity of pembrolizumab, which has the potential to prolong OS in patients with previously treated advanced MSI-H or dMMR CRC with manageable safety. Data from KEYNOTE-164 restart therapy suggested that some patients with disease progression on pembrolizumab could still benefit from restarting pembrolizumab.

The 5-year follow-up results of the CheckMate142 study [19] were reported at 2022 ASCO, a multicohort study, including data on second-line monotherapy, second-line combination therapy, and first-line combination therapy. The results showed that the ORR of different subgroups was consistent with the overall population, and the advantages of PFS and OS in the dual-ICI therapy group were more obvious than those in the monotherapy group, suggesting that dual-ICI therapy may yield better results when the toxicity and cost are not considered.

In the KEYNOTE-177 study, roughly one-third of the patients in the immune monotherapy group had primary drug resistance. It is important to note that dual-ICI therapy can overcome primary drug resistance but also elicit adverse effects. Further follow-up information is needed for CheckMate 8HW (NCT04008030), a phase III confirmatory clinical research study, which examines the effects of dual-ICI therapy, immuno-monotherapy, and chemotherapy in the timmunotherapy response wasreatment of mCRC. Both immuno-monotherapy and dual-ICI therapy can potentially improve the ORR for MSI-H CRC patients receiving postline therapy, with a tendency toward sustainable benefit. However, a longer period of follow-up is required to confirm survival. In addition, the COMMIT study [51] published at the 2022 ASCO meeting was designed to compare the efficacy of atezolizumab monotherapy versus the mFOLFOX6 plus bevacizumab and atezolizumab regimen, which is helpful to clarify whether combined chemotherapy can overcome primary immunotherapy resistance, and the results deserve expecting.

4.2 | Systemic therapy for MSS metastatic CRC

No immunotherapy response was observed in patients with MSS mCRC from the KEYNOTE-016 study [52] or

the KEYNOTE-028 study [53]. Currently, ICI combinations are the main clinical research strategy for MSS CRC. The frequently used combination methods include immunotherapy combined with MEK inhibitors, immunotherapy combined with anti-EGFR antibody, double ICI combination, immunotherapy combined with the tyrosine kinase inhibitor (TKI), and immunotherapy combined with chemotherapy.

4.2.1 | ICIs combined with MEK inhibitors

The phase III IMblaze370 study [54] compared the effectiveness of atezolizumab plus MEK inhibitors cobimetinib versus atezolizumab versus regorafenib in treating patients with chemotherapy-resistant mCRC. With a total enrollment of 363 patients and a median follow-up of 7.3 months, the mOS was 8.87 months in the atezolizumab plus cobimetinib group, 7.10 months in the atezolizumab group, and 8.51 months in the regorafenib group. IMblaze370 did not reach the primary endpoint, with no significant difference in the OS among groups. This study indicated that immunotherapy does not lead to more benefits for mCRC patients with MSS and low baseline levels of immune inflammation.

4.2.2 | ICIs combined with the anti-EGFR monoclonal antibody

Preclinical studies have shown that anti-EGFR therapy can induce tumor-specific immune responses and apoptosis of immunogenic cells [20]. Additionally, anti-EGFR therapy will inevitably lead to the emergence of drug resistance, which is associated with the high expression of CTLA-4 and PD-L1. The LCCC1632 study (NCT03442569) [55], a multicenter, single-arm, and phase II study, was conducted to evaluate the efficacy and safety of panitumumab plus ipilimumab plus nivolumab in patients with "triple wild-type" (KRAS/NRAS/RAF) and MSS mCRC. The study included 56 patients, among whom 49 could be evaluated; the 12-week remission rate was 35% and the mPFS was 5.7 months. The results of the LCCC1632 study suggested that ICIs combined with anti-EGFR therapy for MSS mCRC are worthy of further exploration.

4.2.3 | Dual ICIs combination therapy

The CCTG CO.26 study [56] was a phase II study that aimed to compare durvalumab plus tremelimumab plus best supportive care versus best supportive care alone in patients with advanced refractory CRC. The mOS of the durvalumab plus tremelimumab group and the best supportive care group was 6.6 and 4.1 months, respectively (HR = 0.72, 90% CI: 0.54–0.97), and the mortality ratio in the MSS subgroup was 0.66 (90% CI: 0.48–0.89). This is the first study to demonstrate the effectiveness of a dual-target combination of immunotherapy in MSS mCRC. Still, the improvement in OS was limited, with only a 23% reduction in the risk of death, with no observable trailing effect of immunotherapy onset. Some data suggest that the proportion of patients with TMB ≥ 10 in MSS CRC is 14% [57], but the proportion of MSS CRC with TMB > 20 in the CCTG CO.26 study was 42%, which may be one reason why positive results were achieved and the benefit is still very limited. Future research should focus on using TMB to identify immunotherapy candidates to prevent resource waste and adverse reactions. However, there may be some variations in TMB across different detection platforms, and more work is required to harmonize them.

Anti-CTLA-4 antibodies could block the inhibitory function between CTLA-4 and its ligands CD80 and CD86, acting as a negative regulator of immune activation. A new-generation FC-enhancing immunoglobulin G1 antibody of a newer generation called botensilimab (AGEN1181) has demonstrated remarkable activity in activating both innate and adaptive immune responses. Expansion data from the phase Ib C-800 study [58] suggested that the ORR of dual-ICI therapy was 24% (95% CI: 14%–39%) in 41 evaluable patients at a median follow-up of 5.8 months (1.6–24.4 months) and the DCR was 73% (95% CI: 58%–84%). At the data cutoff, 30% of objective responses had been ongoing for more than a year, and 80% were still in progress. The results of the exploratory analysis demonstrated that patients ($n = 24$) without liver metastases responded better to the combination therapy, with an ORR of 42% (95% CI: 25%–61%) and DCRs of 96% (95% CI: 80%–99%). The novel dual-ICI therapy (botensilimab plus balstilimab) showed excellent response rates, durability, and tolerance, and these results support further development of this combination in MSS CRC patients and in patients with other treatment-resistant tumors.

The LAG-3 inhibitor is another popular ICI target for tumor therapy, which can bind to LAG-3 on T cells to restore the effector function of depleted T cells. The combination of PD-1 inhibitors and LAG-3 inhibitors can activate T cells, promote tumor cell death, and improve immune responses. In a phase III study of MK-4280A (a combination of favezelimab [MK-4280] and pembrolizumab [MK-3475]) versus standard treatment for CRC patients with previously treated and metastatic PD-L1 (+), the results showed that the novel LAG-3 blocking

antibody (MK4280) combined with pembrolizumab had shown preliminary antitumor activity in the postline treatment of MSS mCRC with PD-L1 CPS ≥ 1 [59–62]. Similarly, two phase III clinical studies on LAG3 targets in CRC are also in progress. The release of LAG-3 research results is expected to bring surprises and change the clinical practice.

4.2.4 | ICIs combined with TKI

A phase II study of the multitarget TKI lenvatinib plus pembrolizumab in previously treated patients with solid tumors showed that 32 patients received treatment in the CRC cohort, with an mOS of 10.6 months (95% CI: 5.9–13.1) and an ORR of 22% (95% CI: 9–40) [41]. This combination showed promising antitumor activity and manageable safety. The phase III LEAP-017 study [63] of pembrolizumab plus lenvatinib or standard third-line therapy with regorafenib or TAS-102 in pMMR/non-MSI-H patients is currently underway, and this head-to-head comparison is highly anticipated. It also suggests that the combination of ICIs and TkIs may bring new hope for advanced MSS CRC.

Another MAYA study [64] provided proof of concept that the hypermutation induced by temozolomide can lead to durable remission in MSS and MGMT-silenced mCRC patients treated with low-dose ipilimumab plus nivolumab, with an ORR of 42% and an mPFS of 7.1 months. Further conclusions deserve expecting.

4.2.5 | ICIs combined with chemotherapy

The METIMMOX study [65] was a study of repeat sequential oxaliplatin-based chemotherapy (FOLFOX) plus nivolumab versus FLOX in the first-line treatment of patients with MSS mCRC. The results suggested that patients with MSS mCRC can benefit from immunotherapy through oxaliplatin-based chemotherapy. Yet, the final results seemed to indicate that the efficacy of immunotherapy combined with chemotherapy is hardly better than that of chemotherapy alone. The MEDITREME study [66] evaluated the efficacy of duvalumab plus tremelimumab plus FOLFOX as the first-line treatment for patients with RAS mutated and MSS mCRC, but the results showed that the mPFS of combination therapy was similar to the PFS of dual-drug chemotherapy plus targeted therapy, both of which was 8.4 months. The AtezoTRIBE study [67] explored the efficacy of four drugs combined with atezolizumab as the first-line treatment, and the results showed that the PFS was improved from 11.5 to 13.1 months (HR = 0.69, 80% CI: 0.56–0.85, $p = 0.012$). In the MSS subgroup, PFS was improved from 11.4 to 12.9 months (HR = 0.78, 80% CI: 0.62–0.97, $p = 0.071$). More importantly, there was no significant increase in the occurrence of AEs with atezolizumab, suggesting the potential feasibility of this strategy.

5 | CONCLUSIONS AND PERSPECTIVES

Chemotherapy still plays an important role in the treatment of CRC, although few new chemotherapy drugs have emerged in recent years. However, the basis of chemotherapy has been explored in the optimization mode of mCRC populations with different targets, in combination with traditional molecular targeted drugs such as anti-EGFR monoclonal antibodies or VEGF inhibitors. Consistent with previous data, the results of the CAIRO5 study [68] published in 2022 ASCO confirmed that FOLFOXIRI plus bevacizumab was superior to dual-agent chemotherapy plus bevacizumab in patients with initially unresectable CRCLMs and right-sided primary tumors and/or RAS/BRAF V600E mutation, but it increased the toxicity of treatment at the same time. Consistent with the previous studies of FIRE-3, 80405, and PARADIGM, anti-EGFR treatment of left-sided CRC with wild-type RAS/BRAF showed more benefits in terms of high ORR, rapid deep tumor reduction, and long-term survival, but the PFS was similar to that of anti-VEGF treatment.

A growing body of evidence suggests that CRC is a heterogeneous group of diseases with distinct molecular characteristics that arise from a series of genetic changes. The Cancer Genome Atlas and other genomic studies have provided extensive information on the gene mutations involved in CRC, leading to the identification of potential drug targets and biomarkers. As a major signaling pathway in the development and progression of CRC, the RAS–RAF–MEK pathway has been the main target exploration direction for molecular therapy of mCRC.

The emergence of molecularly targeted drugs for the KRAS gene mutation has broken through the previous dilemma and opinion that KRAS is an undruggable target. KRAS G12C inhibitors alone or in combination with the anti-EGFR monoclonal antibody have shown significant antitumor activity in the treatment of refractory mCRC in initial clinical studies. Clinical studies targeting KRAS G12D, which has a higher mutation probability, are also underway. In the meantime, studies of BRAF-mutant mCRC care ongoing, and the BEACON study continues to update survival

follow-up data. Compared with traditional chemotherapy, regardless of triple-target (EGFR/BRAF/MEK) or dual-target (EGFR/BRAF) inhibition of the RAS–BRAF–MKE pathway, both achieved a significant increase in the definite ORR and a significant improvement in OS. In addition, the BRAF inhibitor (encorafenib) combined with the anti-EGFR antibody (cetuximab) and the anti-PD-1 antibody shows a synergistic antitumor effect in the postline treatment for mCRC patients with MSS and the BRAF V600E mutation, and its efficacy is worthy of further exploration.

Co-inhibition of important upstream and downstream genes can further improve the response rate compared with single-driver gene inhibition in drug studies for both CRC with BRAF V600E and KRAS G12C mutations. In the future, it is possible to adopt a similar combined inhibition mode of upstream and downstream targets in the same signaling pathway or choose the combined inhibition of different signaling pathways, such as RAS/BRAF pathway inhibition combined with WNT pathway inhibition. Cetuximab, the earliest molecularly targeted treatment for CRC, may promote a move back to where it was initially targeted—against the antiepidermal growth factor receptor—as a result of the combined inhibition pattern of targets.

HER-2 is a transmembrane receptor in the epidermal growth factor receptor family. Overexpression of HER-2 is usually caused by gene amplification, leading to the proliferation, invasion, and metastasis of tumor cells. Studies have shown that dual HER2 blockade is an effective HER2-targeting agent for mCRC.

Despite the limited number of drugs available for mCRC, particularly for precisely targeted therapy, the search for new targets remains essential. Certain targets have shown a relatively high expression in CRC and play a role in the development of the disease, making them potential candidates for therapeutic intervention.

Immunotherapy has improved the overall prognosis of metastatic dMMR/MSI-H CRC, having advanced to the level of locally advanced neoadjuvant therapy for patients with dMMR/MSI-H CRC. However, immunotherapy still struggles to be effective in treating MSS/pMMR CRC patients. According to preclinical studies, immunotherapy resistance in MSI-H/dMMR CRC patients may be overcome by combining ICIs with other medications or biological agents. Several clinical studies, including AVETUX, AVETUXIRI, and CAVE, have suggested the prospect of synergistic application of cetuximab and immunotherapy. The combination of PD-1 inhibitors with other targeted drugs such as multitarget kinase inhibitors is also the director of clinical development. In addition, the combination of the anti-PD-1 antibody and new ICIs like LAG-3 has shown preliminary therapeutic effects.

In summary, improving the immunogenicity of tumors while also increasing the targeting of the immune system and improving the invasiveness of immune cells have become crucial strategies to improve the effectiveness of immunotherapy in treating CRC patients. Future research will focus heavily on the use of chemotherapy in conjunction with targeted therapy, oncolytic viruses, CAR-T therapy, tumor vaccines, and checkpoint inhibitors to enhance the efficacy of treatment.

AUTHOR CONTRIBUTIONS

Dan Su: Writing—original draft (equal); writing—review and editing (equal). **Chao Liu:** Writing—original draft (equal); writing—review and editing (equal); formal analysis (lead). **Jie Cui:** Writing—review and editing (supporting); software (equal). **Jiebing Tang:** Writing—review and editing (supporting). **Yuli Ruan:** Writing—review and editing (supporting); software (equal). **Yanqiao Zhang:** Conceptualization (lead); supervision (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

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